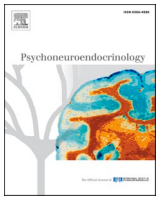
Psychoneuroendocrinology 142 (2022) 105772

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



A systematic review and meta-analysis of the Everyday Discrimination Scale and biomarker outcomes

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ARTICLE INFO

Keywords:
Social discrimination
C-reactive protein
Inflammation
Telomere length
Stress

ABSTRACT

Discrimination has consistently been associated with multiple adverse health outcomes. Like other psychosocial stressors, discrimination is thought to impact health through stress-related physiologic pathways including hypothalamic-pituitary-adrenal (HPA) axis activation, dysregulation of inflammation responses, and accelerated cellular aging. Given growing attention to research examining the biological pathways through which discrimination becomes embodied, this systematic review and meta-analysis synthesizes empirical evidence examining relationships between self-reported discrimination and four biomarker outcomes (i.e., cortisol, C-reactive protein (CRP), interleukin-6 (IL-6), and telomere length) among studies that have used the Everyday Discrimination Scale. We conducted a systematic review of studies discussing self-reported, everyday, or chronic discrimination in the context of health by searching Medline / PubMed (National Library of Medicine, NCBI), PsycInfo (APA, Ebsco) and Web of Science Core Collection (Clarivate). Twenty-five articles met the criteria for meta-analysis, with several reporting on multiple outcomes. Discrimination was associated with elevated CRP levels ($r = 0.11$; 95% CI: 0.01, 0.20, $k = 10$), though not cortisol ($r = 0.05$; 95% CI: −0.06, 0.16, $k = 9$), IL-6 ($r = 0.05$; 95% CI: −0.32, 0.42, $k = 5$), or telomere length ($r = 0.03$; 95% CI: −0.01, 0.07, $k = 6$). We identify several points of consideration for future research including addressing heterogeneity in assessment of biomarker outcomes and the need for longitudinal assessments of relationships between discrimination and biomarker outcomes.

1. Introduction

In addition to the inequitable access to opportunities, resources, and power due to structural oppression at structural, cultural, and institutional levels, discrimination acts as the behavioral expression of oppression, resulting in inequitable treatment for marginalized groups (Priest et al., 2020a; Tajfel and Turner, 2004). As one of the most frequently assessed domains of discrimination, self-reported discrimination is often conceptualized as a stressor that adversely affects health, with a large proportion of the literature examining the impacts of

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https://doi.org/10.1016/j.psyneuen.2022.105772
Received 2 September 2021; Received in revised form 1 March 2022; Accepted 17 April 2022
Available online 21 April 2022
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self-reported racial discrimination (Dolezsar et al., 2014; Gilbert and Zemore, 2016; Goosby et al., 2018; Krieger, 2014; Lewis et al., 2015, 2014; Pascoe and Smart Richman, 2009; Williams et al., 2019a, 2019b; Williams and Mohammed, 2009). The study of discrimination as a type of psychosocial stressor that adversely affects health and as a contributor to race/ethnic disparities in health has grown in the last two decades (Krieger, 2014). A recent review documented 29 reviews of the literature that were published between 2013 and 2019 which examined relationships between discrimination and mental and physical health outcomes (Williams et al., 2019b). Most early research on the relationship between discrimination and health documented associations with mental health, indicators of health behavior, or self-reported measures of physical health (Williams and Mohammed, 2009). However, research has begun to elucidate the biological pathways through which societal and psychosocial stressors, like discrimination, are embodied to affect health (Cuevas et al., 2020; Priest, 2021).

A growing body of evidence suggests that experiences of discrimination may affect physical and mental health through multiple biological pathways (Clark et al., 1999; Epel, 2009; Lewis et al., 2015). The conceptual model of allostatic load, developed by McEwen and Stellar, suggests that frequent exposure to psychosocial stressors – such as discrimination – results in the activation of multiple axes involved in the stress response, e.g., the neuroendocrine system (HPA axis, sympathetic-adreno-medullar axis), the autonomic nervous system, immune and inflammatory processes, and metabolism (McEwen, 2000; McEwen and Stellar, 1993; Seeman et al., 2001). As a result of societal processes of social marginalization and devaluing, individuals from marginalized groups experience increased exposure to discrimination which is posited to be embodied through the activation of HPA axis (i.e., cortisol) and inflammation (i.e., interleukin-6 and C-reactive protein) cascades or accelerated cellular aging (i.e., shortened telomere length). These outcomes capture distinct, but inter-related processes through which discrimination may affect health. These systems interact with each other, suggesting a coordinated physiological response to stress. For example, chronic elevation of HPA axis and inflammation mediators result in interactions which yield chronic elevations in blood pressure that can contribute to adverse cardiovascular outcomes such as heart attacks and stroke (McEwen, 2008). Much of the literature supports this framework, with researchers identifying relationships between discrimination and increased HPA axis activation, (Clark et al., 1999) dysregulation of inflammatory responses, (Cuevas et al., 2020) and accelerated cellular aging. (Epel, 2009) Studies have also found biomarkers associated with these pathways (e.g., cortisol, CRP, telomere length) to have documented associations with increased morbidity across several health outcomes and mortality (Cuevas et al., 2020; McEwen, 2008, 2012).

Indeed, closer examination of the relationship between discrimination and biomarkers provides an opportunity to advance our mechanistic understanding of how chronic experiences of differential treatment become embodied or "get under the skin" to contribute to poor psychological and physiological health (Krieger, 2005; McEwen, 2012). The use of biomarkers measures also circumvents the issue of common source bias that may arise when both the exposure (discrimination) and health outcome are self-reported. However, a comprehensive assessment of the association between experiences of discrimination and biomarkers of physiologic stress, inflammation, and accelerated aging has not been performed to date.

Studies assessing biological pathways are a small proportion of the total literature on discrimination but are increasing in recent years. A recent systematic review of discrimination and systemic inflammation identified 28 articles published since 2009 (Cuevas et al., 2020). These measures were not included in previous meta-analyses of the health implications of discrimination. Prior meta-analyses have examined the relationship between discrimination and health across several measures of discrimination, with much heterogeneity in the timing and type of discrimination experienced (Paradies et al., 2015; Pascoe and Smart Richman, 2009; Pieterse et al., 2012). Results from previous meta-analyses suggest that the associations between discrimination and health outcomes vary by instruments used to assess discrimination (Dolezsar et al., 2014; Paradies et al., 2015). Reducing heterogeneity in meta-analysis by limiting variations across measures of discrimination, for example, is also important statistically when combining estimates across studies in meta-analysis (Bourabain and Verhaeghe, 2021; Imrey, 2020).

The larger literature on stress and health suggests that incidents of racial discrimination, like other self-reported stressors, can be classified into several types of stressful life experiences (Williams and Mohammed, 2009). Similar to research on stress and health, interpersonal experiences of discrimination can be divided into acute major discriminatory life events (e.g. being unfairly fired from a job), chronic discrimination in major domains life (e.g. at work, school, or in one's neighborhood), traumatic discriminatory experiences (e.g. being beaten by the police) and more minor but ongoing events, somewhat analogous to daily hassles in the larger stress literature (Williams and Mohammed, 2009). Different measures of discrimination assess various aspects of these stressful experiences. The Everyday Discrimination Scale (EDS) captures only the latter class of relatively minor, but recurrent instances of discrimination (Williams et al., 1997). Enhancing our understanding of the ways in which discrimination can affect health requires greater research attention to understanding how specific types of discrimination are related to health outcomes. Social Identity Theory provides a framework that allows for an understanding of how social contexts and identities facilitate differential treatment, devaluing, and withholding of resources by members of the "in-group" can result in the disadvantage that members of marginalized groups face. (Tajfel and Turner, 2004) In this context, marginalized groups are more likely to encounter experiences of discrimination, which have long been theorized to be "assaults to [B]lack dignity and [B]lack hope [that] are incessant and cumulative" in their adverse impacts on health (Pierce, 1974). Understanding the everyday encounters of discrimination marginalized groups face facilitates an understanding of how recurrent exposure to differential treatment becomes embodied and how the EDS remains a strong predictor of the onset and progression of adverse health outcomes (Kershaw et al., 2016a; Lewis et al., 2006; Williams et al., 2003).

A sufficient number of studies have been conducted utilizing the EDS to permit a review of the association of discrimination with biomarkers (i.e., HPA axis, inflammation, and cellular aging). To the authors' knowledge, this is the first meta-analysis that examines the association of discrimination on stress-related biomarkers among studies that have used the same measure. Accordingly, this paper sought to synthesize existing literature, provide deeper insight into methodological and measurement challenges, and identify future research directions.

1.1. Study objectives

This systematic review and meta-analysis examined the relationship between experiences of discrimination and molecular biomarker outcomes, with quantitative focus on interleukin-6 (IL-6), CRP, cortisol, and leukocyte telomere length, among studies that have used the EDS to measure exposure to discrimination. We characterized the existing body of literature that has included the EDS – highlighting study design and methodology, sample characteristics, operationalization of the EDS, and outcomes examined. We examined relationships between the EDS and individual biomarker measures of stress, inflammation, and cellular aging (e.g., telomere length) – to increase the comparability of findings across studies that have used the same assessment of exposure to discrimination.

Specifically, the overarching research aims of the systematic review were to:

1. Meta-analyze associations between the EDS and stress-related biomarkers. We hypothesize that increased discrimination is associated

with adverse levels of biomarker measures (i.e., shorter telomere length; higher IL-6, CRP, and cortisol levels).
2. Descriptively map the mediators (e.g., smoking, excess drinking) of the associations between discrimination and molecular biomarkers across studies that have used the EDS. This provides context as to what factors have been considered as mediating variables in studies assessing discrimination and biomarker outcomes.

2. Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and criteria (Moher et al., 2009; Stroup et al., 2000).

2.1. Search strategy

Studies discussing self-reported, everyday, or chronic discrimination in the context of health were identified by searching Medline / PubMed (National Library of Medicine, NCBI), PsycInfo (APA, Ebsco) and Web of Science Core Collection (Clarivate). Controlled vocabulary terms (i.e., MeSH; Thesaurus of Psychological Index Terms) were included when available and appropriate. The search strategies were designed and executed by a research librarian (CM) at the Countway Library of Medicine at Harvard University. Publication date was limited to studies published in 1997 or later. No language restriction was applied. The exact search terms used for each of the databases are provided in the Supplementary materials (Supplemental Table 1). Reference lists of identified papers were examined for additional relevant articles for inclusion.

2.2. Inclusion criteria

For consideration of inclusion, studies must have used quantitative methodology reporting an estimate of the relationship between the EDS and a disease-related molecular biomarker (e.g., telomere length, IL-6) (Broza et al., 2019; Epel, 2009; Laterza et al., 2007). As such, studies using qualitative methods were not included. All collection methods for molecular biomarkers were included (e.g., blood, saliva, hair, urine) (Broza et al., 2019). All study designs were eligible (i.e., cross-sectional, longitudinal, case-control, and experimental). Given that the EDS was first utilized in 1997, (Williams et al., 1997) studies were eligible for inclusion if published in 1997 or later.

Exclusion restrictions were not placed upon study populations, such that studies including participants from any age group, racial/ethnic/cultural identity, ability, and other sociodemographic factors were included.

2.2.1. Exposure

Self-reported discrimination was measured using the EDS, which includes the frequency of self-reported discrimination in the respondent's day-to-day life (Williams et al., 1997) The original scale includes nine-items: "In your day-to-day life, how often do any of the following things happen to you?" (1) You are treated with less courtesy than other people are; (2) You are treated with less respect than other people are; (3) You receive poorer service than other people at restaurants or stores; (4) People act as if they think you are not smart; (5) People act as if they are afraid of you; (6) People act as if they think you are dishonest; (7) People act as if they're better than you are; (8) You are called names or insulted; and (9) You are threatened or harassed. Responses for each item include "almost every day," "at least once a week," "a few times a month," "a few times a year," less than once a year," and "never". Respondents reporting "a few times a year" or more frequent experiences of discrimination may be asked a follow up question: "What do you think is the main reason for these experiences?" Participants can select one or more of the following attributions: (1) your ancestry or national origins; (2) your gender; (3) your race; (4) your age; (5) your religion; (6) your height; (7) your weight; (8) some other aspect of your physical appearance; (9) your sexual orientation; (10) your educational or income level.

A short form of the EDS was developed for the Chicago Community Adult Health Study (CCAHS) (Sternthal et al., 2011) in which respondents were asked: ""In your day-to-day life, how often have any of the following things happened to you?" (1) You are treated with less courtesy or respect than other people; (2) You receive poorer service than other people at restaurants or stores; (3) People act as if they think you are not smart; (4) People act as if they are afraid of you; (5) You are threatened or harassed. The follow-up question and response categories of the shortened EDS are the same as the original. Other adapted versions of the scale were considered eligible for inclusion if they were not major adaptations beyond the original scope of the EDS (e.g., studies that created summary scores that joined the EDS with other measures or studies that only include one item from the EDS were not included).

2.2.2. Outcomes

All stress-related biomarker outcomes were eligible for inclusion. These included IL6, CRP, cortisol, DHEA (dehydroepiandrosterone, also DHEA-S), DNA methylation, E-selectin, fibrinogen, nerve growth factor, alpha amylase, HSP-70 (heat shock protein-70), HbA1c levels, and telomere length.

Several outcomes were only examined in one or two articles and were excluded from the meta-analysis but are included in our narrative synthesis of the findings (N = 5, Fig. 1). For example, DNA methylation was only assessed as an outcome in two identified studies. The three remaining outcomes meeting the inclusion criteria were only assessed in one manuscript each.

2.3. Screening

Search results were imported into Endnote X9, and duplicate entries were removed. The Endnote library was exported into Covidence (Veritas Health Innovation, 2017), a web-based systematic review software. Two reviewers (JL, GM) independently conducted title and abstract screening to assess studies for eligibility (inter-reviewer reliability (κ) = 0.78, indicating good agreement).

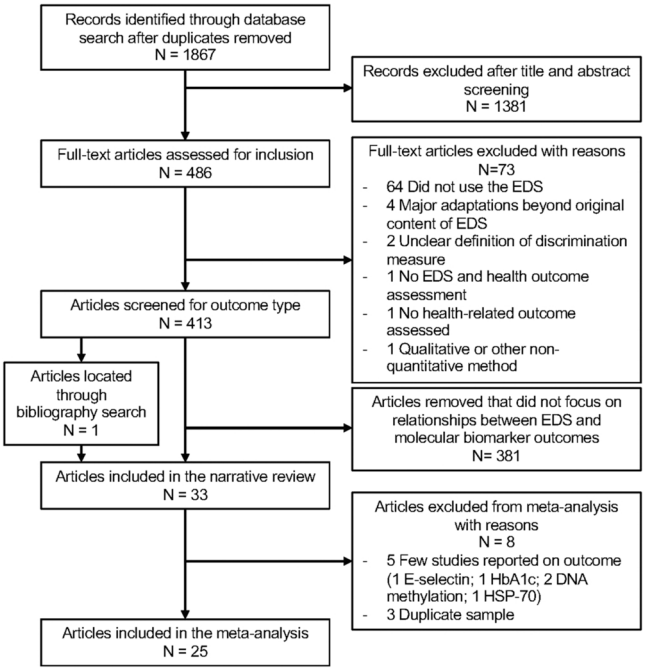

Fig. 1. Study identification and selection process.

Full texts of studies considered for inclusion were obtained. Discrepancies between reviewers regarding study inclusion was resolved by discussion with a third reviewer (HC) and/or consensus (JL, GM) [$\kappa = 0.74$]. The study selection process is outlined in full in Fig. 1.

2.4. Data extraction and analysis

Data from identified studies were independently extracted into an Excel document by one reviewer (JL) with another reviewer randomly checking 20% of the extracted data (HC). Inconsistencies were resolved by consensus and/or discussion with a third reviewer (GM). Extracted data included information regarding the EDS (e.g., version used, operationalization) and biomarker assessed, demographic characteristics of participants (e.g., age, gender, educational attainment), study attributes (e.g., study design, location [country and region], period and duration of study (if relevant), sample size), most and minimally adjusted estimates, covariates adjusted for, psychometric properties of the scale (if assessed), mediators (if explicitly mentioned) and potential sources of bias (e.g., attrition, missing data). For articles using the same dataset to examine relationships with the same outcome, we extracted data from papers with the most information reported (e.g., both minimally and fully adjusted models reported). If multiple papers included the same amount of information, the earliest publication was included in the meta-analysis.

Minimally adjusted estimates include data from the least adjusted model reported or correlations between EDS and biomarkers. Fully adjusted estimates include data from the most adjusted model reported with all covariates included. Efforts were made to contact study authors for additional information; however, if only one estimate was available, it was used as both the minimally and most adjusted estimate.

Most studies reported regression coefficients. To incorporate regression coefficients into the present meta-analysis, we use a derived formula developed by Peterson and Brown to estimate correlation coefficients (r) (Peterson and Brown, 2005). After extracting over 1500 β and r values, the authors fit several models to assess the relationships between the two measures. They found that $r = 0.98\beta + 0.05\lambda$ yielded the best fit, where β is the coefficient reported and λ is an indicator variable that is 0 when β is negative and 1 when β is positive (Peterson and Brown, 2005). After testing this efficacy of this formula against several alternatives, the authors found little difference between results. However, the authors note that this imputation is best used among β estimates within the interval of − 0.50–0.50, given an observed tight joint distribution of β and r values in that range. Given that most estimates from eligible studies were within that range, we imputed r values from reported β values in eligible studies where r values were not reported using $r = 0.98\beta + 0.05\lambda$.

Estimates were coded such that greater experiences of discrimination are associated with poorer outcomes (negative for telomere length, positive for inflammation and stress biomarkers (e.g., IL-6)).

Weighted correlation sizes were calculated using large-sample approximation to compute sampling variance (Viechtbauer, 2010). Random effects models were fit utilizing the minimally adjusted associations reported using the “metafor" package (Viechtbauer, 2010) available in R (R Core Team, 2013). Random effect models essentially relax the assumption of fixed-effect models, which assume that there is one ”true” effect estimated in all studies and that variations only occur due to chance (i.e., variations in samples) (Borenstein et al., 2010). Instead, random effects models assume a distribution of correlation sizes allowing for variations in the correlation size across studies, where factors beyond sampling variation may influence the association (e.g., age of sample) (Borenstein et al., 2010). Cochran’s Q test was conducted to test for heterogeneity. Forest plots are presented to illustrate study-specific and overall correlation sizes by outcome and 95% CIs. Sensitivity analyses included estimating the weighted correlation sizes using the most adjusted estimates reported in eligible articles.

2.5. Quality assessment

Study quality was assessed in terms of potential for bias. Similar to Paradies et al. (2015), we use sampling procedure, data type (e.g., cross-sectional, longitudinal), and instrument (i.e., full scale, short form), and covariates included in a narrative assessment of study quality. Funnel plots were created to illustrate potential publication bias and asymmetry was tested using Egger’s tests (Egger et al., 1997).

3. Results

Database searches on 03/24/2020 yielded 2803 references, resulting in 1867 unique references for screening. Relevant outcomes were found in 33 articles included in the narrative review and 25 studies were identified for inclusion in the quantitative synthesis of associations in the present study. The number of studies excluded from the quantitative analysis, with reasons, are provided in detail in Fig. 1. Overall descriptive data for the articles included in the quantitative assessment are summarized in Supplemental Table 2.

Most studies were published between 2016 and March 2020, with all articles having publication dates between 2010 and 2020. Nearly all articles examined associations among populations in the United States, with one assessing associations among a sample in New Zealand. Nearly 36% of studies implemented representative sampling procedures, with 64% of studies reporting non-representative sampling methods. Many articles reported findings from cross-sectional analyses (72%) with the remainder being longitudinal (24%) or other (4%).

Sample sizes ranged from 49 to 12,624, with a total sample of 37,763 respondents included across all eligible studies. All articles reported some information on participant age (e.g., average age of population), race/ethnicity, and sex; however, two did not report the number of participants within each racial/ethnic group in the analytic samples. Articles were mostly conducted among adults (nearly 99% of the sample size), though populations under 18 were included in three articles, yielding 419 young adult or adolescent participants (< 18 years of age) to the total sample. One study did not report the age range of study participants to discern whether young adults could have been included in the study population. Data on participant educational attainment was reported in 19 studies.

The full version of the EDS was employed in most articles (N = 17), with fewer using the short-form (N = 5) or a modified version of the EDS (N = 3). Attribution of experiences was assessed in 7 studies, with most assessing attributions of experiences to both racial and non-racial reasons (N = 4). The remaining three studies that captured attributions assessed only racial or non-racial attributions. Operationalization of the EDS remained consistent across studies with most measuring experiences as the sum (N = 11) or the average (N = 10) of the frequency of experiences. Other means of operationalizing the EDS included a count of yes responses to experiences, dichotomizing beyond a certain threshold. How the measure was operationalized was unclear in one analysis. Among studies that examined the reliability of the EDS, it exhibited very good reliability using a Cronbach’s alpha cutoff of greater than 0.80 in 18 of the 25 articles.

Cortisol and CRP were the most frequently assessed biomarker outcomes (N = 9 and N = 10, respectively), followed by telomere length (N = 6) and IL-6 (N = 5). Approximately 16% (N = 4) of articles reported associations between the EDS and multiple biomarker outcomes.

Supplemental Table 3 presents the summary of study and sample characteristics by outcome. Weighted correlation sizes from the most adjusted associations reported between the EDS and each biomarker outcome are presented in Figs. 2–5.

3.1. Cortisol

Nine studies examined relationships between discrimination and cortisol. Most frequently, the EDS was operationalized as the mean

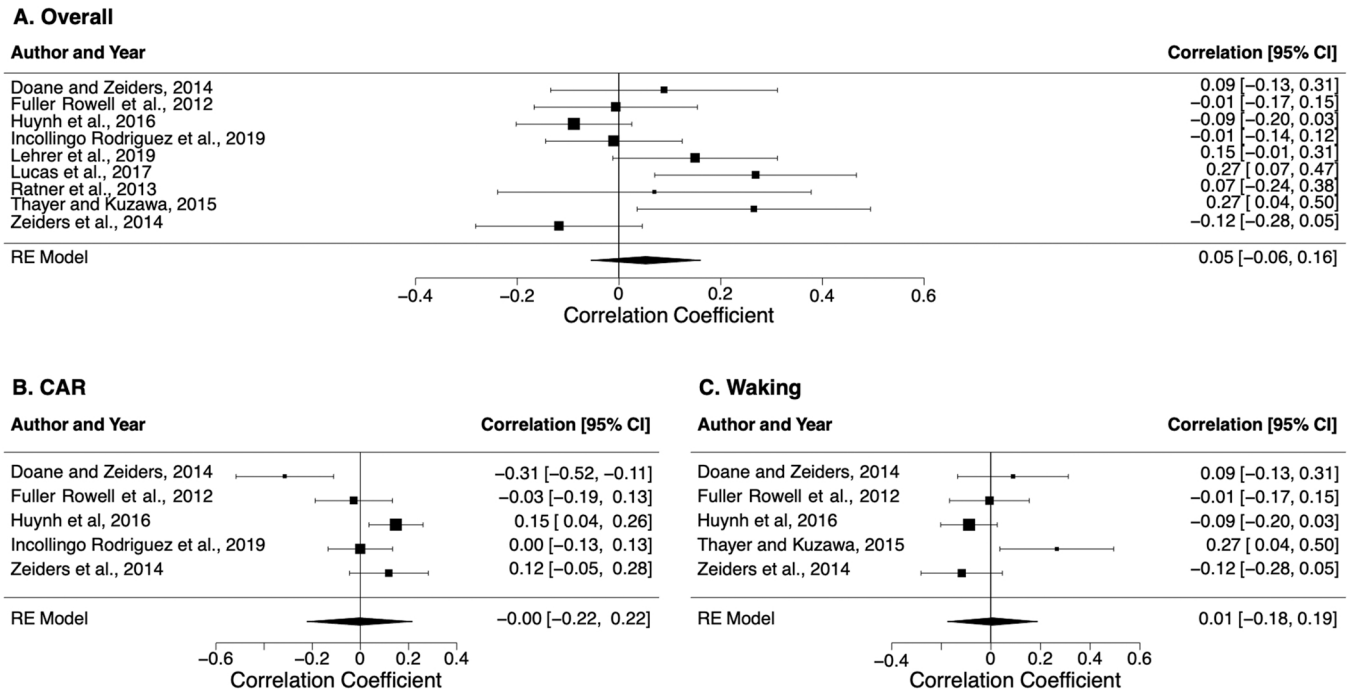

Fig. 2. Associations between EDS and (a) all cortisol outcomes; (b) cortisol awakening response (CAR); and (c) waking levels (minimally adjusted).

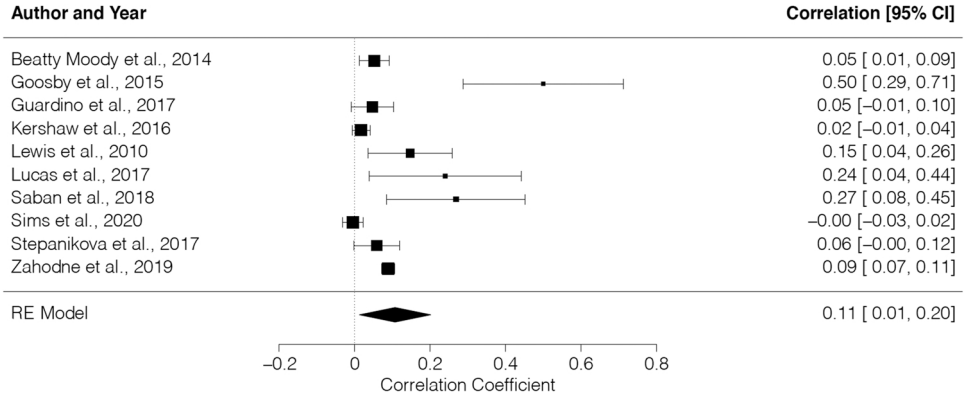

Fig. 3. Associations between EDS and C-reactive protein (CRP, minimally adjusted).

(N = 4) or sum of frequencies (N = 3). Another study used the count of yes responses, though one study did not clearly specify how the measure was operationalized. Studies were primarily cross-sectional (N = 7) and conducted among adults (N = 6). Black participants comprised nearly 29.4% of the cortisol study population, followed by Latinx/Hispanic (18.6%) and Asian (7.7%) participants; however, white participants (38.6%) comprised the largest proportion of the study population across all 9 studies. Native Hawaiian, Pacific Islander, or Māori, multiracial, and individuals categorized as "other" racial groups together comprised the remaining 5.7% of the pooled study population.

Assessments of cortisol varied across studies. Given the evidence of changes in cortisol levels throughout the day, (Levine et al., 2007; Weitzman et al., 1971) some studies assessed salivary cortisol by collecting multiple samples per day at different time points (≥4) over several days (≥3) (Doane and Zeiders, 2014; Fuller-Rowell et al., 2012; Huynh et al., 2016; Zeiders et al., 2014). Others collected two saliva samples (morning and evening) over two consecutive days Thayer and Kuzawa, 2015), three salivary samples in one day, (Incollingo Rodriguez et al., 2019) salivary samples before, during and after exposure to a stress task (Lucas et al., 2017) and the average of duplicate samples collected in one afternoon (Ratner et al., 2013). Another study assessed cortisol concentration through hair cortisol, using 3 cm of hair closest to the scalp to assess retrospective cortisol levels (Lehrer et al., 2020). In the main analysis, the reported assessment of cortisol levels varied, with articles assessing associations between the EDS and waking cortisol levels in five studies, baseline cortisol, average cortisol from one measurement, total daily cortisol, and hair cortisol concentration. Five studies reported both minimally and fully adjusted estimates, while the remaining reported only unadjusted (N = 2) or adjusted (N = 2).

The mean correlation coefficient for associations between EDS and cortisol was $r = 0.05$ [95% CI: − 0.06, 0.16, k = 9; Q= 19.83, df= 8, p = 0.011] (Fig. 2A), suggesting no observed association with cortisol levels. Patterning in the direction of responses was observed, where larger studies showed null or negative associations while smaller studies typically had associations indicating greater cortisol levels with increased discrimination. Minimally adjusted models included four correlations and models that accounted for factors including age, race, sex or gender, BMI, socioeconomic indicators (i.e., household income, educational attainment, material deprivation), health behaviors (i.e., exercise, food, alcohol and caffeine consumption, cigarette use), daytime sleep, daily wake and sleep time, psychological factors (i.e., stress level, emotional stability), and medication (i.e., cortisol medication,

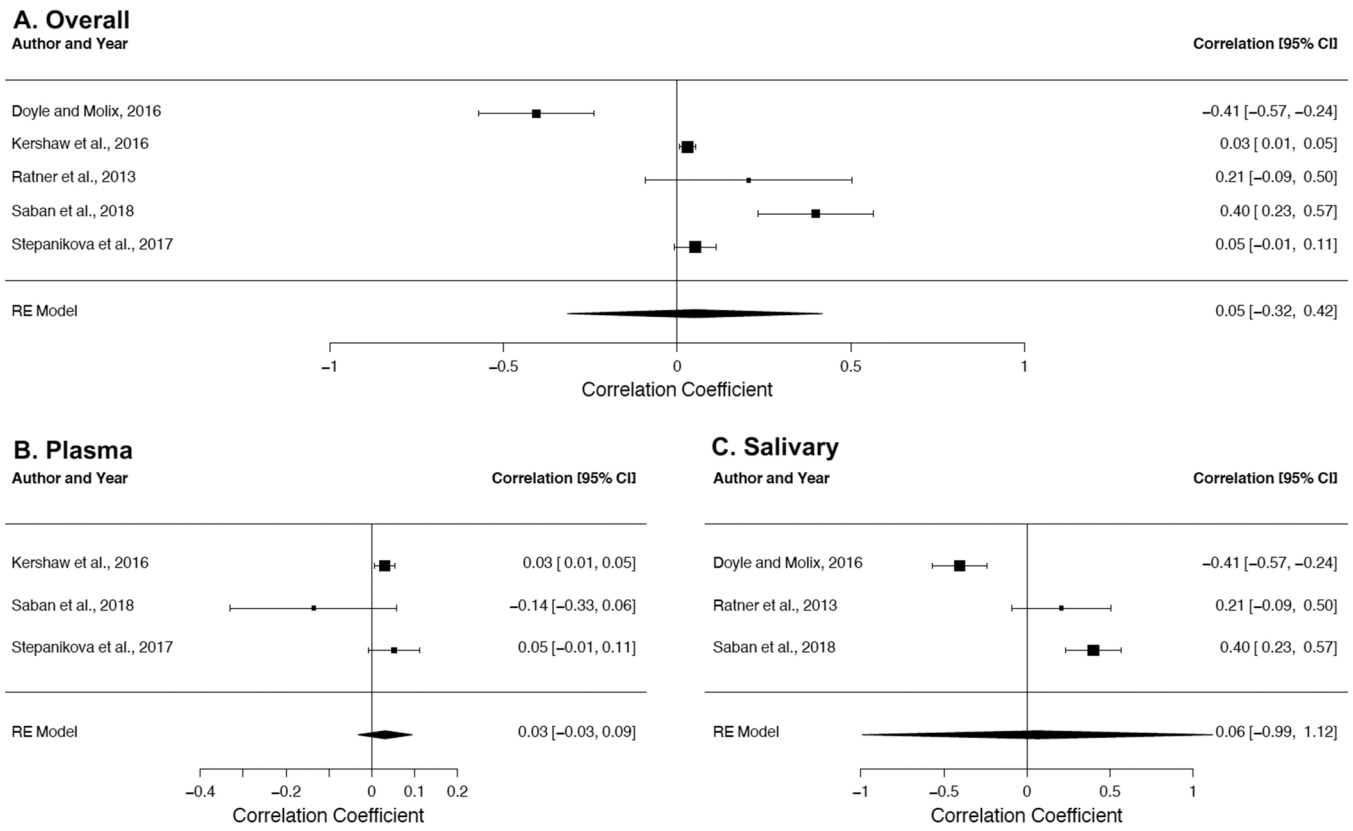

Fig. 4. Associations between EDS and (a) interleukin-6 (IL-6) across all studies; (b) plasma samples; and (c) salivary samples (minimally adjusted).

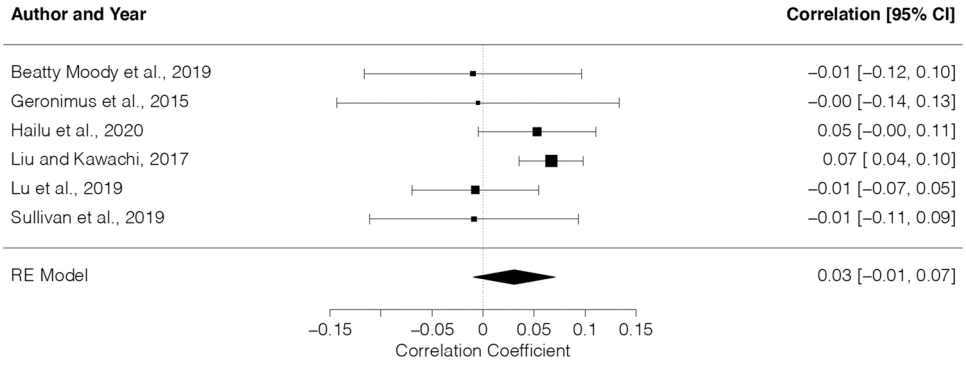

Fig. 5. Associations between EDS and telomere length (minimally adjusted).

other medication use) or medical history (i.e., C-section delivery).

Several studies reported estimates between the EDS and cortisol outcomes using the same measure (i.e., cortisol awakening response [CAR], waking levels). To minimize the impact of heterogeneity in the measurement of cortisol on the pooled estimate, we estimated mean correlation sizes for studies that examined the CAR (Doane and Zeiders, 2014; Fuller-Rowell et al., 2012; Huynh et al., 2016; Incollingo Rodriguez et al., 2019; Zeiders et al., 2014) (defined as the change in cortisol from waking to a defined time period after waking) and waking cortisol levels (Doane and Zeiders, 2014; Fuller-Rowell et al., 2012; Huynh et al., 2016; Thayer and Kuzawa, 2015; Zeiders et al., 2014). Among studies that evaluated the relationship between the EDS and waking cortisol, the mean correlation size was $r = 0.01$ (Fig. 2B, *95% CI: −0.18, 0.19*). Whereas the mean correlation size among studies reporting associations between the EDS and CAR was $r = 0.00$ (Fig. 2B, *95% CI: −0.22, 0.22*). These findings suggest that discrimination is not associated with cortisol levels, specifically waking and the cortisol awakening response.

Sensitivity analyses were conducted using the most or fully adjusted estimates reported in each study. The mean correlation size did not differ greatly across fully adjusted estimates ($r = 0.06$; *95% CI: −0.06, 0.18*) compared to the minimally adjusted models. Associations between discrimination and CAR ($r = 0.02$; *95% CI: −0.24, 0.29*) and waking cortisol ($r = 0.00$; *95% CI: −0.19, 0.18*) remained null. Beyond covariates included in the minimally adjusted models, fully adjusted models also included factors such as psychological factors (i.e., neuroticism risk, public and private esteem), average hours of sleep, medication (i.e., contraceptive use), waist-to-hip ratio, and attributions of discrimination.

3.2. C-reactive protein (CRP)

Among the ten eligible studies assessing the association between discrimination and CRP, the EDS was frequently implemented as the sum (N = 5) or mean (N = 4) of the frequencies of experiences of

discrimination. One study operationalized the EDS as the sum of the experiences (Lewis et al., 2010). Nine of the ten studies reported the racial/ethnic composition of the analytic samples, with 38% identifying as Black, 7% as Latinx/Hispanic, 2% as Asian and 52% as white/-European. A small percentage of participants were classified as "Other" race (1%). Most studies were cross-sectional in design (50%) and conducted among adult populations (N = 9). CRP was assessed consistently, with most studies using blood/serum levels of CRP (N = 9) and one using a measure of salivary CRP levels.

The pooled correlation size for the associations between discrimination and CRP was $r = 0.11$ *[95% CI: 0.01, 0.20; k = 10; Q* = 69.90, df= 9, $p < 0.001$*]*. Correlation sizes appear to be larger in smaller studies, though larger studies also show relationships between discrimination and CRP. Minimally adjusted estimates included one unadjusted correlation and models which accounted for factors such as age, race/ethnicity, lifetime experiences of discrimination, measures of socioeconomic status (e.g., income, educational attainment, employment status), BMI and medications (e.g., statin use, hormone replacement therapy, anti-inflammatory use). Three articles did not report unadjusted associations, (Beatty Moody et al., 2014; Saban et al., 2018; Zahodne et al., 2019) though one only accounted for age, BMI and statin use in the adjusted estimate reported (Saban et al., 2018).

Supplemental Fig. 2 illustrates the reported associations and mean correlation size using the most adjusted estimates reported. Significant associations were observed [$r = 0.09$; 95% CI: 0.01, 0.17, $k = 10$]. These associations remain considering the covariates included in the most adjusted models reporting these associations. One paper only reported a minimally adjusted association (correlation), however other articles accounted for factors such as race, age, sex, BMI, measures of socioeconomic status (e.g., financial strain, educational attainment, income), psychological factors (e.g., depressive symptoms, cynicism) and lifetime experiences of discrimination, health behaviors (e.g., physical activity, smoking, alcohol consumption), measures of physiological functioning (e.g., blood pressure, cholesterol and triglyceride levels, HbA1c, vital capacity, adiponectin), health conditions (e.g., heart attack, other vascular diseases, diabetes), and medications (e.g., statin use, antihypertensives, diabetes management medications). The similarities in mean correlation sizes from the most and minimally adjusted estimates reported suggest that the relationship between discrimination and CRP is robust to covariate adjustment and may not be strongly mediated by health behaviors (e.g., smoking, drinking).

3.3. Interleukin-6 (IL-6)

Among the 5 studies examining IL-6, the EDS was operationalized as the sum of frequencies (N = 3) or mean of frequencies (N = 2). White/European participants comprised over 80% of the sample across studies reporting data on race/ethnicity (N = 4). Measurement of IL-6 levels was captured through blood (N = 3) or saliva (N = 3). One study assessed both blood and salivary IL-6 levels, though only the adjusted association was reported for the blood IL-6 outcomes (Saban et al., 2018). Eligible studies used in the meta-analysis were all cross-sectional in design and conducted among adult populations.

The mean weighted correlation size between discrimination and IL-6 suggests discrimination may not be correlated with elevated IL-6 levels ($r = 0.05$; 95% CI: −0.32, 0.42, k = 5; Q = 47.01, df = 4, $p < 0.001$). Minimally adjusted estimates included an unadjusted correlation (N = 1) and models (N = 4) that accounted for factors such as race/ethnicity, gender, age, measures of socioeconomic status (i.e., income, educational attainment, employment status), medication use (i.e., anti-inflammatory, hormone replacement therapy), and time. Larger correlation sizes were observed among two smaller studies; while one association went in the opposite direction, indicating an inverse relationship between discrimination and IL-6 levels.

Additionally, when assessed by measurement of IL-6 (i.e., plasma, salivary), we find the direction of the mean correlation size for the minimally adjusted estimates to be similar among both measures ($r = 0.03$; *95% CI: −0.03, 0.09* and $r = 0.06$; *95% CI: −0.99, 1.12* for plasma and salivary measures, respectively). However, the confidence interval is larger among studies using salivary measures of IL-6, possibly indicating greater variability in estimates derived from salivary samples. These assessments should be interpreted with caution given the small sample size for these assessments (k = 3 for each) and that one study reported only fully adjusted associations between discrimination and plasma IL-6 levels.

Supplemental analysis of the most adjusted estimates reported resulted in a stronger correlation between increased experiences of discrimination and IL-6 levels [$r = 0.07$; 95% CI: − 0.28, 0.42, $k = 5$], however, the confidence interval is wide and crosses the null. Examining the forest and tree plot, we observed null associations in studies of varying sample sizes (two, relatively large and one small), though the remaining two studies find lower and elevated IL-6 levels to be associated with increased discrimination. The observed null associations may be a function of covariates included in each model. In most adjusted models, several studies accounted for what could be potential mediators or moderators of the relationship between discrimination and IL-6 levels. Covariates included age, race, marital status, measures of socioeconomic status (i.e., income, employment status, educational attainment), psychological factors (i.e., measures of depression, anxiety, reactivity), perceived social status, reported childhood trauma, medication use (i.e., cholesterol, blood pressure, diabetes, hormone replacement), public and private esteem, BMI, and alcohol consumption.

Mediators. One study explicitly assessed BMI as a potential mediator of the relationship between discrimination and IL-6 in a sample of men and women (Kershaw et al., 2016b). Among women, the authors found the positive relationship between everyday discrimination and IL-6 to be attenuated by BMI. However, the inability to establish temporality given the cross-sectional analysis does not provide insight as to whether BMI is subsequent to exposures to discrimination or whether it may increase experiences of discrimination (Kershaw et al., 2016b).

3.4. Telomere length

Three of the six eligible studies operationalized the EDS as the sum of reported frequency of discrimination. Assessments also included the mean of frequency of experiences of discrimination (N = 2) and a dichotomized assessment of if a respondent ever experienced everyday discrimination and attributed it to a personal characteristic (yes/no). The racial/ethnic breakdown of analytic samples were provided in 5 of the 6 studies, with white participants comprising 60% of the overall study populations. Black participants comprised approximately 33% of the overall sample size, followed by Latinx/Hispanic participants (7.4%). Asian, Native Hawaiian/Pacific Island, multiracial or "Other" racial/ethnic individuals were not represented in the studies eligible for inclusion. All eligible studies used quantitative polymerase chain reaction (qPCR) to assess and quantify telomere length, which is optimal for large studies given the small sample needed to replicate DNA and assess telomere length (Montpetit et al., 2014). Additionally, all studies utilized leukocyte samples to ascertain telomere length. Three studies examined associations between discrimination and telomere length using the ratio of telomeric length of DNA to a single-copy control gene (T/S ratio) which is correlated with telomere length, (Hailu et al., 2020; Liu and Kawachi, 2017; Lu et al., 2019) while others converted the T/S ratio to kilobase or base pairs to compare differences in length (Beatty Moody et al., 2019; Geronimus et al., 2015; Sullivan et al., 2019).

Everyday discrimination was not associated with telomere length when minimally adjusted models were assessed ($r = 0.03$; *95% CI: −0.01, 0.07, k = 6; Q*=7.26, df = 5, p = 0.202*)*. Examining the forest and tree plot, we observe that most studies indicate a null association, with larger studies finding discrimination to be associated with longer telomere length. Minimally adjusted estimates included unadjusted

regression coefficients (N = 2), estimates from an age-adjusted model (N = 1), and two adjusted estimates that accounted for age, race, sex, measures of socioeconomic status (i.e., poverty-to-income ratio; educational attainment); and psychosocial stress (i.e., safety stress, physical environment, and negative social interactions).

Supplemental analyses of fully adjusted estimates exhibited similar associations. The mean correlation size using the most adjusted estimates reported were not statistically significant [r = 0.02; 95% CI: − 0.02; 0.06]. Models accounted for factors such as age, race, sex, measures of socioeconomic status (i.e., poverty-to-income ratio; educational attainment); and psychosocial stress (i.e., safety stress, physical environment, negative social interactions, perceived stress); psychological factors (i.e., depression, reaction type); smoking status; BMI; health conditions (e.g., diabetes, hypertension, myocardial infarction, cancer), Census region of birth; childhood health; lifetime substance use and physical activity.

Mediators. Two studies explicitly examined potential mediators of the relationship between discrimination and telomere length. Work by Liu and Kawachi assessed whether physical activity, smoking status, and having a BMI $\geq$ 30 kg/m^2 mediated the relationship between discrimination and telomere length (Liu and Kawachi, 2017). The authors found evidence that suggested these factors mediate the relationship between everyday discrimination and telomere length, observing attenuated associations when these factors were included in regression analyses. Sullivan et al. examined whether depressive symptoms and perceived stress mediated the relationship between discrimination and telomere length (Sullivan et al., 2019). The authors found that observed associations between everyday discrimination and telomere length among Black and white women remained after accounting for mediating variables, with correlation sizes remaining larger (i.e., shorter telomere length) for Black women; though no associations were observed among men.

Across three of the four analyzed outcomes, between study heterogeneity was high and statistically significant as measured by the Cochran's Q test. Results from the Q-test reject the null hypothesis of the "true" effect being the same across studies and only differing due to sampling variability, indicating that other factors may influence biomarker outcomes.

3.5. Quality assessment

The limited availability of longitudinal assessments of the relationship between the EDS and biomarker outcomes leaves us unable to assess the temporality of associations. Across all outcomes, most studies were cross-sectional (77.8%, 50%, 100%, and 100% for cortisol, CRP, IL-6, and telomere length respectively). Several studies utilized nonrepresentative sampling procedures (N = 7, 7, 3, and 1 for cortisol, CRP, IL-6, and telomere length, respectively). This may raise concerns regarding potential bias such that correlation sizes may be estimated from samples that may not be generalizable, however they do provide context to the experiences of individuals from similar backgrounds (i.e., communities with similar sociodemographic characteristics). However, most studies assessing representative samples contributed greater weights to the estimated mean correlation size given the small variances across all outcomes. Most studies used the full EDS or short form (N = 8, 10, 4, 4), with few utilizing modified versions. Among studies reporting the Cronbach's alpha (N = 22), α was greater than or equal to 0.70 suggesting acceptable or better internal consistency of the measure. Studies reporting adjusted models accounted for several socioeconomic, demographic, and health-related covariates that may confound the relationship between discrimination and biomarker outcomes. Adjusted models sometimes accounted for potential mediators of the relationship (i.e., perceived stress) that may have partially accounted for the effect of discrimination.

3.6. Assessment of publication bias

Funnel plots (Fig. 6) and Egger's tests were used to evaluate the possibility of publication bias. Among studies that examined cortisol, eligible studies tended to have smaller standard errors, but eligible studies had positive, negative, and null associations. Results from the Egger's test to assess funnel plot asymmetry in funnel plots were not statistically significant (t = 1.91, df = 7, p = 0.098), suggesting that the funnel plot for cortisol is not imbalanced (i.e., no publication bias). Assessment of the funnel plot for CRP outcomes appears to be asymmetric. Eligible studies tend to have small standard errors or larger correlation sizes. Results from the Egger's test were statistically significant (t = 4.57, df = 8, p = 0.002), suggesting potential publication bias. Fewer studies examined IL-6 and telomere length. The funnel plot for IL-6 appears to be relatively symmetric, with eligible studies having variations in correlation size and standard error. One study was included that documented associations in the opposite direction for IL-6 (i.e., lower IL-6 levels for increased report of discrimination). Eligible studies examining telomere length had varying directions (i.e., null, and positive associations reported). The Egger's test for IL-6 was not statistically significant, suggesting that publication bias may not be a concern (t = 0.30, df = 3, p = 0.785); however, Egger's test for telomere length was significant (t = −3.00, df = 4, p = 0.040) indicating the possibility of publication bias. These results should be interpreted with caution as the Egger's test has limited power when used in a small sample of studies.

3.7. Narrative review

Five studies that were relevant to our review but were not included in the meta-analysis are narratively synthesized here. Friedman et al. found that everyday discrimination was associated with greater E-selectin levels, an indicator of inflammation response, among men, but not women in a sample of adults in the Midlife in the United States study (MIDUS) (Friedman et al., 2009). Using data from a community sample of adults with poorly controlled type 2 diabetes, Potter et al. found that everyday discrimination attributed to weight was associated with elevated HbA1c levels (Potter et al., 2015). Relationships between everyday discrimination and DNA methylation, an indicator of stress, were assessed in two studies (Santos et al., 2018; van der Laan et al., 2020). Among a sample of Latina mothers, Santos et al. found that everyday discrimination was inversely associated with DNA methylation (less methylation with increased discrimination), (Santos et al., 2018) while van der Laan et al. found everyday discrimination to be positively associated with DNA methylation among participants in the Research on Obesity and Diabetes among African Migrants (RODAM) study (van der Laan et al., 2020) Saban and colleagues examined the relationship between several social factors – including everyday discrimination – and heat shock protein-70 (HSP-70), another stress-related biomarker, in a small sample of Black and white women with atherosclerosis (Saban et al., 2014) The authors did not observe an association between discrimination and HSP-70 levels, though this association should be examined in a larger study population.

4. Discussion

Though previous meta-analyses have examined the relationship between discrimination and several health outcomes, variations in the measurement of discrimination have made cross-study comparisons difficult. Evidence from the most recent meta-analysis suggests that the relationship between discrimination and health outcomes vary according to the measure of discrimination used (Paradies et al., 2015). This current systematic review and meta-analysis is the first to standardize the measure of discrimination to assess the association of discrimination and health by restricting the analysis to studies that have used the Everyday Discrimination Scale. These findings also contribute to the

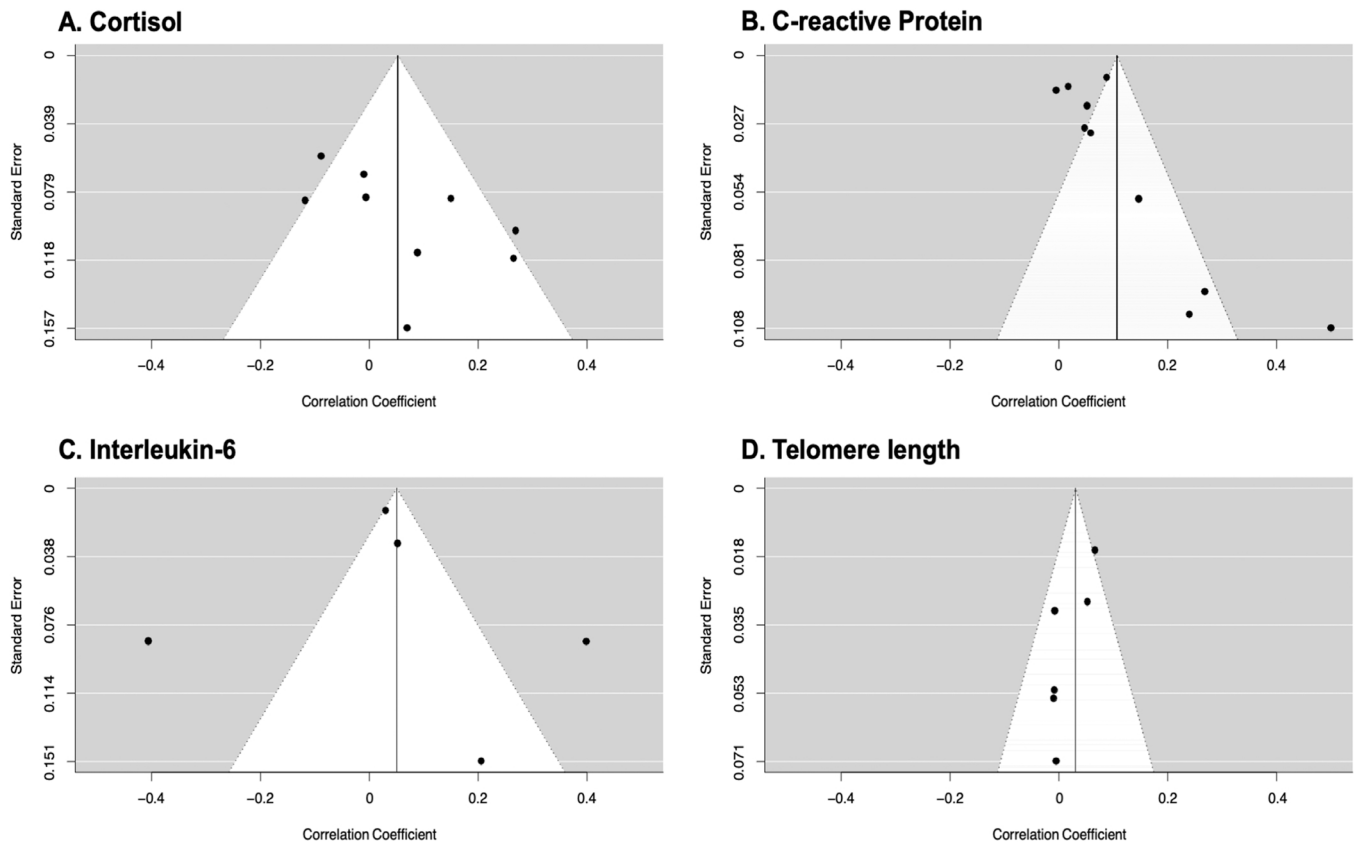

Fig. 6. Funnel plots for A) cortisol; B) CRP; C) IL-6; and D) telomere length.

literature by estimating the pooled correlation coefficient across studies that have examined the relationship between discrimination and molecular biomarkers of stress, inflammation, and cellular aging.

We found that most eligible studies operationalized the EDS as the mean or sum of reported frequency (N = 21 of 25). Our findings also suggest that increased self-report of discrimination is associated with higher CRP levels, though we did not observe evidence of associations between discrimination and cortisol, IL-6, or telomere length when using the EDS. We also observed patterns in the magnitude of associations by sample size. For example, larger positive correlation sizes were observed among two smaller studies examining associations between the EDS and IL-6 while more modest positive correlations were observed among two larger studies. One small study had a large negative association, which may have influenced the null finding for IL-6.

Null associations between discrimination and cortisol and telomere measures were not surprising as neither of these biomarkers have been consistently associated with other types of stress (Chida and Steptoe, 2009; Fogelman and Canli, 2018; Korous et al., 2017; Mathur et al., 2016). However, we identified associations between discrimination and CRP, consistent with associations observed in other systematic reviews and meta-analyses of self-report measures and stress tasks (Cuevas et al., 2020; Steptoe et al., 2007). The correlation of discrimination with higher CRP, but not IL-6 suggests that more studies are needed on the latter, given that IL-6 stimulates the production of CRP (Papanicolaou et al., 1998). This may also reflect a need to examine alternative measures of cumulative and chronic inflammation, such as glycoprotein acetyls (GlycA), instead of acute phase inflammatory markers (Priest, 2021). However, studies have identified both IL-6 and CRP to have independent relationships with several adverse health outcomes and risk factors (Bermudez et al., 2002; Pradhan et al., 2001).

We noted three factors (1) heterogeneity in outcome measurement; (2) study design; and (3) sample demographics that could have contributed to our mixed findings. First, the observed findings between discrimination and cortisol, IL-6, and telomere length may be influenced by several factors related to outcome measurement. Specifically, eligible studies differed in their operationalization of biomarker outcomes. Among studies that examined cortisol, differences in both the number of samples captured and cortisol outcomes assessed (e.g., momentary cortisol, hair cortisol concentration) were observed. For example, heterogeneity may be introduced by including hair cortisol in this analysis given that hair samples capture cortisol levels over a period ranging from several weeks to months (Iob and Steptoe, 2019). Additionally, cortisol levels fluctuate throughout the day, typically with higher levels at waking and lower during the evening (Levine et al., 2007; Weitzman et al., 1971) and are sensitive to the method of collection (i.e., blood, saliva) (Levine et al., 2007). Collecting sufficient data to understand individual cortisol fluctuations and utilizing measures of diurnal cortisol may be useful contributions to future research (Adam et al., 2017).

We also observed differences in how inflammation was assessed among eligible studies assessing IL-6. IL-6 samples were collected through blood (N = 3) or saliva (N = 3), with one study assessing both. While the mean correlation size across studies that used either measure was similar ($r = 0.03$; $r = 0.06$, plasma and saliva respectively), we observed a wider confidence interval across studies using salivary assessments. This could reflect greater variability in salivary assessments of IL-6; however, the intervals may also be wide given the limited number of studies available. These differences suggest consideration of the means of assessment of inflammatory markers. This is especially relevant given that salivary assessments of inflammation may capture oral rather than systemic inflammation (Priest et al., 2020b). Previous research has concluded that plasma and salivary samples of inflammatory biomarkers (i.e., IL-6, CRP) may not be strongly correlated, and that blood samples – though relatively invasive – are preferred to salivary measures to assess systemic inflammation (Cullen et al., 2015; Williamson et al., 2012).

Optimal assessments of telomere length are still being explored. All

eligible studies used qPCR to assess telomere length which has several strengths that have been summarized in detail elsewhere (Montpetit et al., 2014). These strengths include that qPCR requires a small sample of DNA, is easily implemented in large studies, and has a reference to compare samples to. However, this method is sensitive to the quality of the DNA sample and the reference is not standardized which makes cross-study comparisons difficult (Montpetit et al., 2014). Additionally, qPCR provides an estimate of the telomere amplification product (T) as compared to that of a reference single-copy gene (S) (Aviv et al., 2011; Montpetit et al., 2014). This is used to create a T/S ratio that correlates with average telomere length, but does not yield a base pair estimate (Montpetit et al., 2014). While qPCR has been widely accepted as an approach to assess telomere length, other techniques exist to determine telomere length (Montpetit et al., 2014). These include flow-fluorescence in situ hybridization (FISH) and Southern blot, which is often referred to as the golden standard (Aviv et al., 2011). The FISH method is labor intensive and is likely not useful for large scale epidemiologic studies, as obtaining needed samples can be difficult compared to qPCR and Southern blot (Aviv et al., 2011; Montpetit et al., 2014). However, both qPCR and Southern blot yield reproducible results though the measurement error is greater in qPCR analyses (Aviv et al., 2011). Both qPCR and Southern blot come with a set of tradeoffs that should be explored regarding their ability to impact cross-study comparisons. Across all biomarkers used, differences in sample types and quality, frequency of measurement, as well as methodology used highlight a need to identify "gold standard" measures of biomarker levels and implement consistency in biomarker operationalization across studies.

Second, study design may have influenced our findings. Several studies employed non-representative sampling. This may reflect populations that are more or less likely to report experiences of discrimination and are willing to have their biomarkers sampled (e.g., have a blood draw) which is likely to introduce further selection bias. While these findings may not be generalizable to a broader population, they still provide insight into the experiences of individuals and communities with similar characteristics. The preponderance of cross-sectional studies in our review limits the ability to establish a temporal order between exposure to discrimination and biomarker changes, although the use of biomarkers reduces the possibility of reverse causality (i.e., people are generally unaware of their levels of circulating inflammatory biomarkers and hence biomarkers are unlikely to influence reports of discrimination). The longitudinal assessment of experiences of discrimination also makes it possible to examine trajectories of experiences over time and the cumulative impacts of discrimination on biomarker outcomes. Priorities for future research on discrimination and health include the need for more longitudinal assessments and representative sampling, particularly of marginalized groups that may be most susceptible to experiencing discrimination and the differential health, social, and economic burden of such experiences.

Though not quantifiable in the present analysis given the limited number of studies, findings from individual studies suggest there may be heterogeneity in the associations of discrimination and biomarkers according to race/ethnicity, gender, and/or sexual orientation (Doyle and Molix, 2016; Kershaw et al., 2016b; Ratner et al., 2013; Saban et al., 2018). Specifically, studies that examined associations among marginalized groups observed more nuanced associations than the average correlation obtained from our pooled estimates. For example, Lehrer et al. found that everyday discrimination was associated with hair cortisol concentration among Black participants, though not white participants (Lehrer et al., 2020). Differential relationships among marginalized groups may be obscured in assessments where their experiences are not centered or when included in study populations where those groups are less represented. These relationships should be explored in future research. Additionally, while the literature on discrimination and health is global and spans across the lifecourse, (Paradies, 2006; Williams et al., 2019b) assessments of the association between discrimination and biomarkers that use the EDS have been predominantly carried out in the United States (N = 24) and among adult populations. Associations between discrimination and biomarkers should be examined in other national contexts and lifecourse periods to assess comparability. While the underlying mechanisms may not differ, cross-context studies can help to elucidate causal mechanisms and effect modifiers useful to understanding relationships between discrimination and health. Associations between discrimination and biomarkers across the lifecourse may vary at different periods (i.e., early life, adolescence, mid-life, older age). Relatedly, items in the EDS may not perform the same in different countries and populations. For example, to extend the use of the measure, the EDS has recently been adapted for Aboriginal and Torres Strait Islander peoples to capture experiences and attributions relevant to Indigeneity in Australia (Thurber et al., 2021).

It should also be noted that there is a body of literature that suggests that psychosocial factors and coping strategies may influence reports and impacts of experiences of discrimination (Berjot and Gillet, 2011; Brondolo et al., 2009; Pascoe and Smart Richman, 2009). Unhealthy coping strategies (e.g., suppressing responses) or "negative" psychosocial factors have maintained fairly consistent associations with worsened health impacts of discrimination, (Brondolo et al., 2009; Himmelstein et al., 2015; Krieger and Sidney, 1996; Nuru-Jeter et al., 2009) though findings regarding the overall health impacts of active or health-promoting coping strategies and positive psychosocial factors have been mixed (Brondolo et al., 2009; James, 1994; Pascoe and Smart Richman, 2009). While insight into how individual-level coping behaviors and resources is useful and can inform individual-level interventions, the focus should extend beyond the individual-level. Though these measures may be useful in understanding how marginalized people respond to and cope with discrimination – and should be further explored – focus on individual coping strategies without intervening on the structural and cultural factors that pattern these experiences may do little to mitigate adverse health outcomes and sustain wellbeing (Bailey et al., 2020, 2017; Homan, 2019; James, 1994).

Our search found that CRP, cortisol, IL-6, and telomere length were outcomes that were assessed with reasonable frequency. However, in addition to studies in the meta-analysis, the narrative review revealed a broader range of biomarkers for future research. In addition to those identified in our narrative synthesis of relevant papers, several inflammatory markers such as IL-1β, TNF-α, and inflammatory mechanisms such as the Conserved Transcriptional Response to Adversity (CTRA) have been identified in a recent review of the relationship between discrimination and inflammation (Cuevas et al., 2020). Measures such as GlycA may be more accurate measures of cumulative inflammation and have been associated with several chronic and acute health outcomes in adults (Priest, 2021). This literature suggests that future research should examine relationships between discrimination and these understudied indicators of biological functioning to better understand and intervene upon the health implications of societal conditions and contexts.

While future research should increase focus on relationships between discrimination and biomarkers (as well as potential interventions), it should also consider whether these associations differ when other measures of discrimination are used (e.g., Experiences of Discrimination, (Krieger, 1990; Krieger and Sidney, 1996) Major Experiences of Discrimination Scale, (Williams et al., 1997) or Schedule of Racist Events (SRE) (Landrine and Klonoff, 1996)). Studies using the Experiences of Discrimination (EOD) scale have found positive associations with IL-6 levels (Giurgescu et al., 2016). A cross-sectional analysis by Chae and colleagues found the main effect of EOD on telomere length to be null in a sample of Black men (Chae et al., 2014), though, in a recent longitudinal assessment, they found evidence of greater 10-year telomere shortening among a sample of Black adults in the CARDIA study (Chae et al., 2020). Differences in findings of these assessments may reflect differences in 1) study design (i.e., cross-sectional vs. longitudinal) or 2) study population (e.g., middle-aged Black men in the Bay Area vs. a broader sample of middle-aged Black adults across 4 cities). Research examining the relationship between discrimination using the

SRE and cytokine levels (i.e., indicators of inflammation) found increased discrimination to be associated with elevated cytokines (Brody et al., 2015; Simons et al., 2021). An eligible study also assessed associations between discrimination and telomere length using the Major Experiences of Discrimination Scale finding null associations (Hailu et al., 2020). It seems that the direction of relationships is relatively consistent across measures, though these are comparisons to individual studies. However, each measure captures different domains and frequencies in which discrimination occurs and offers considerations of different policy suggestions and interventions to mitigate their impacts. Future research estimating the pooled correlation size between various indicators of discrimination and biomarker outcomes across studies that use measures that capture different forms, severity, and specific attributions of discrimination could contribute to understanding how discrimination adversely affects indicators of health status across the continuum of disease. It may also be useful to understand whether these associations differ among measures of discrimination that do not rely on the willingness of an individual to report compared to those which require self-report (Krieger et al., 2010). Additionally, this work can contribute to an evidence base that emphasizes the importance of policy and programs in tandem with research to intervene prior to the development of diseases to prevent and reduce disease burden among marginalized groups.

The present meta-analysis is not without its limitations. In examining the relationship between discrimination and biomarkers using the EDS, we rely on a measure of discrimination that captures general experiences of unfair and differential treatment. While useful, the EDS is distinct from measures that capture discrimination occurring within institutional contexts (e.g., the EOD scale), those that capture specific forms of oppression (e.g., the SRE), measures that capture discrimination as a result of an individual's multiple marginalized identities (e.g., Multiple Discrimination Scale (Bogart et al., 2010)), and those capturing experiences which result in material, opportunity, and political deprivation irrespective of whether an individual was aware of such experiences and reported them as discriminatory or harmful (Bailey et al., 2017; Krieger, 2011, 2012; Williams and Mohammed, 2009). Additionally, we only include findings from published manuscripts, which may differ from associations reported in unpublished works. Specifically, results from the Egger's test suggests publication bias among studies that assessed CRP, though not for cortisol, telomere length, or IL-6. This may reflect a trend of not publishing null findings for CRP and may also reflect the need for more research on IL-6, telomere length, and cortisol given the smaller number of studies identified. We estimated mean correlation sizes from minimally adjusted associations reported in each article, however we also examine associations reported in most adjusted models to account for potential confounders of the association.

The biomarkers included in our review are linked with each other, resulting in a cascade of physiological responses to stress. For example, chronic inflammation (measured through IL-1β and IL-6) may lead to shortened telomeres, (Baylis et al., 2014) acting as a potential mediator between discrimination and telomere length. However, our review did not consider the complex, inter-relationships between biomarkers representing different systems. Instead, we have focused on summarizing the associations with individual components of the stress response, as well as reveal gaps in the evidence.

This study also has several strengths. It quantifies the relationship between discrimination and molecular biomarkers, which provide evidence for some of the pathways that discrimination may become embodied. We also examine the relationship among studies that use the same measure of discrimination, the EDS, thus increasing the comparability across studies. The EDS is a widely used measure in both domestic and international contexts. Full, abbreviated, or modified versions of the EDS are included in many major epidemiologic studies in the United States and elsewhere (See for example: (Bild et al., 2002; Heeringa and Connor, 1995; Jackson et al., 2004; Radler, 2014; Rosenberg et al., 1995; Steptoe et al., 2013; Taylor et al., 2005; Williams et al., 2004)). The frequent inclusion of EDS in cross-national studies to examine the implications of discrimination on health allows for the systematic examination of the strength of associations between discrimination and health using a standardized exposure. Additionally, the utility of the EDS in capturing, reasonably accurately, the experiences of discrimination has been documented across a wide range of populations, with good internal consistency and validity (Gonzales et al., 2016; Kim et al., 2014; Krieger et al., 2005; Lewis et al., 2012). We also evaluate, where possible, the relationship between discrimination and biomarkers among studies that have utilized similar means of outcome assessment (i.e., CAR, waking cortisol, blood, and salivary IL-6) to further increase the comparability across studies.

Overall, our results provide information on the relationships between discrimination and several molecular biomarkers. The number of studies was limited, but we did find associations consistent with discrimination having an adverse effect, though evidence can be strengthened. There is a need of research using a broader range of biomarkers to better characterize the relationships between discrimination and physiological indicators. This study identifies associations between discrimination and biological indicators that have been identified as possible precursors to adverse health outcomes using a consistent measure of discrimination. We also provide considerations for future research utilizing biomarker outcomes to strengthen ongoing efforts.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Acknowledgements

N/A.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105772.

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